SUPPORT FOR THE AMENDMENTS

Newly-added Claims 37-48 are supported by the specification and the original claims, particularly by Example 1 conducted on a kilogram scale. Accordingly, no new matter is believed to have been added to the present application by the amendments submitted above.

REMARKS

Claims 37-48 are pending, upon entry of the amendments submitted above. Favorable reconsideration is respectfully requested.

Applicants would like to thank Examiner Henry for the helpful and courteous discussion held with their representative on April 8, 2008. During the discussion, Claim 37 submitted above and the submission of an additional Rule 132 Declaration were discussed. The following remarks expand on the discussion with the Examiner.

As set forth in Claim 37, the present invention relates to a process of lyophilization for the preparation of a piroxicam:β-cyclodextrin inclusion compound in a 1:2.5 molar ratio conducted *on a kilogram scale*, comprising:

(a) dissolving piroxicam and β-cyclodextrin in the molar ratio of 1 to 2.5 and ammonium hydroxide in water brought to a temperature of at least 60 °C;

(b) pouring the piroxicam and β-cyclodextrin dissolved in water from (a) on temperature-controlled shelves of a freeze-dryer pre-cooled to a temperature of at least -30 °C to lower the temperature of the solution to -10 °C at a cooling rate equal to or higher than 1 °C/min, to produce a frozen solution;

(c) further lowering the temperature of the frozen solution to at least -20 °C; and

(d) drying the frozen solution under vacuum,

wherein the inclusion reaction is complete with complete amorphization of the inclusion compound and complete conversion of the piroxicam to the zwitter-ionic form.

Thus, the claimed process is performed on a large-scale basis-- i.e., kilogram quantities of reactants.

The rejection of the claims under 35 U.S.C. §103(a) over Chiesi et al. (EP 0153998) is respectfully traversed. The reference fails to suggest the claimed process.

As discussed with the Examiner on April 8, 2008, the Inventors have discovered that when working on an kilogram scale, the cooling of the aqueous solution to the temperature of complete freezing, i.e., -10 °C, should be carried out very rapidly as claimed, i.e., at cooling rate equal to or higher than 1 °C/min. Only this well-defined and controlled cooling rate allows one to obtain a piroxicam:β-cyclodextrin complex characterized by complete inclusion and complete amorphization, where the piroxicam is present in the zwitterionic form.

As recognized by the Office, Chiesi et al. are completely silent regarding the cooling rate of the aqueous solution and it does not contain any teaching on how to achieve complete freezing at a cooling rate equal or higher than 1°C min. In addition, Chiesi et al. fails to describe conducting the reaction on a kilogram scale.

In addition, the executed Rule 132 Declaration submitted herewith demonstrates that when freeze-dryer shelves are pre-cooled to a temperature of -20 °C under the conditions described by Chiesi et al. on a kilogram scale, β-cyclodextrin begins to re-crystallize before the complete freezing of the solution followed by de-complexation of piroxicam and partial loss of the zwitter-ionic structure. See paragraphs 5-7 of the Declaration.

When the temperature reached a value lower than the eutectic temperature of the product (-18°C), the frozen solution containing crystalline β-cyclodextrin was dried under vacuum. The obtained product was analyzed by differential scanning calorimetry (DSC) analysis. The thermal trace showed an endothermal melting peak at 190-200°C typical of crystalline "uncomplexed"piroxicam. A rough estimation of the area of the peak indicates the presence of at least 20-30% of crystalline piroxicam, confirming that the yield of the process is lower compared to the process claimed in the above-identified application, which specifies completeness of the inclusion reaction. See paragraphs 8 and 9 of the Declaration.

Therefore, pre-cooling the shelves of the freeze-dryer to a temperature of -20° C is *not* sufficient for achieving a cooling rate equal to or higher than 1° C/min, and hence for obtaining a product characterized by: i) completeness of the inclusion reaction; and ii) complete amorphization, and wherein piroxicam is present in the zwitter-ionic form, as claimed in the above-identified application. See paragraph 10 of the Declaration.

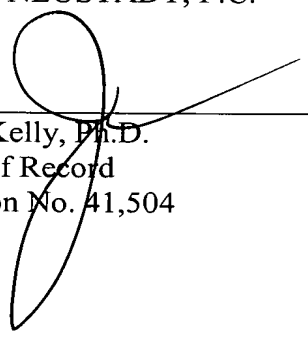
In view of the foregoing, the claimed process is not obvious of Chiesi et al. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The objection to Claim 24 is believed to be obviated by the amendment submitted above. Claim 24 has been canceled.

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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